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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/555,544	11/04/2005	Yoshihiro Ohmiya	2008_0998	9022

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EXAMINER	
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ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/555,544	OHMIYA ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2008 and 11 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *1-6,8,19-21 and 23-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,9-18 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 November 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/08, 1/08, 2/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicant's election without traverse of Group VIII, a red-emitting luciferase gene from rail road worm, a green-emitting luciferase gene from *Rhagophthalmus ohba* and a orange-emitting luciferase gene from *Rhagophthalmus ohba* as the species of three luciferase genes and a constantly-expressed promoter, a toxicity assessing promoter and a promoter subject to assessment as the species of promoters in the replies filed on 2/8/08 and 6/11/08 is acknowledged.

Claims 1-6, 8, 19-21 and 23-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Election was made **without** traverse in the replies filed on 2/8/08 and 6/11/08.

Claims 7, 9-18 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7, 11, 14, and 17 (upon which claims 9, 10, 12, 13, 15, 16, 18 and 22 depend) are indefinite in the recitation of "does not substantially depend on a determining condition" as it is unclear what constitutes a determining condition. The specification on page 13 indicate that determining conditions are pH, temperature, concentration or the like. However, this

is vague and unclear as it does not define what is encompassed by "or the like" nor does it define which compounds concentration is relevant. As the scope or anything which is encompassed beyond pH or temperature is completely unknown for further examination this phrase is interpreted as the "does not substantially depend on pH or temperature".

Claims 9 and 16 are indefinite in the recitation "derived from a rail road worm" and derived from *Rhagophthalmus ohba*" as it is unclear if this is synonymous with "isolated from" or is meant to encompass mutants and variants of luciferases which may be isolated from the recited organisms. If it encompassed mutants and variants, it is unclear how many changes from a luciferase which can be isolated from the recited organisms may be present.

Claim 10 is indefinite in the recitation of "comprising an element for promoting efficiency of translation and/or an element for stabilizing mRNA" as the specification does not define what structural elements are encompassed by these phrases. Page 20 of the specification states that "as the element for promoting the efficiency of the translation, Kozak sequence and the like are exemplified" and "as the element for the stabilization of mRNA, β-globin intron II and the like are exemplified" however, the scope of the phrase "or the like" is

vague and unclear. What sequences beyond a Kozak sequence for the element for promoting efficiency of translation and mammalian introns for the element for stabilizing mRNA are encompassed?

Claim 11 is indefinite in the recitation of "and if necessary a gene …" as neither the claim nor the specification indicate when this element is "necessary".

Claim 18 an 22 are indefinite in the recitation of "toxicity assessing promoter" as this phrase is vague and unclear as to what promoters are encompassed. The specification provides absolutely no explanation of what this encompasses and it is entirely unclear what promoters would be included. In view of the total lack of explanation of this terminology, any promoter different from the other promoters defined by these claims i.e., a constitutive promoter and in claim 18 a promoter subject to assessment is deemed included.

Claims 7, 9-18 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to constructs or host cells comprising said constructs comprising a genus of luciferase genes which emit light having a λ_{max} of 536-635 nm which does not substantially depend on either pH or temperature. The specification teaches the structure of only a few representative species of such luciferases. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a luciferase which emits light having a λ_{max} of 536-635 nm which does not substantially depend on either pH or temperature. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 7, 9-18 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for vectors or cells encoding the luciferases of SEQ ID NOS 2, 4, and 12-15, does not reasonably provide enablement for vectors and host cells comprising any gene encoding luciferase which emit light having a λ_{max} of 536-635 nm which does not substantially depend on either pH or temperature or any red-

emitting luciferase from rail road worm, green-emitting luciferase from rail road worm, green-emitting luciferase from *Rhagophthalmus ohba* or any orange-emitting luciferase from *Rhagophthalmus ohba*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 7, 10-15, 17, 18 and 22 are so broad as to encompass vectors and host cells comprising one or more gene encoding any luciferase which emits light having a λ_{max} of 536-635 nm which does not substantially depend on either pH or temperature and claims 9 and 16 are so broad as to encompass vectors and host cells comprising one or more gene encoding any red-emitting luciferase from rail road worm, green-emitting luciferase from rail road worm, green-emitting luciferase from *Rhagophthalmus ohba* or any orange-emitting luciferase from *Rhagophthalmus ohba* which emits light having a λ_{max} of 536-635 nm which does not substantially depend on either pH or temperature. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of luciferase genes broadly encompassed by the vectors and host cells of the claims. Since the amino acid sequence of a protein determines its structural and functional properties,

predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to only genes encoding the luciferases of SEQ ID NOS 2, 4 and 12-15 and includes absolutely no guidance with regard to structural features which result in the recited functional features of which emits light having a λ_{max} of 536-635 nm which does not substantially depend on either pH or temperature.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish

with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass vectors and host cells comprising any gene encoding luciferase which emit light having a λ_{max} of 536-635 nm which does not substantially depend on either pH or temperature or any red-emitting luciferase from rail road worm, green-emitting luciferase from rail road worm, green-emitting luciferase from *Rhagophthalmus ohba* or any orange-emitting luciferase from *Rhagophthalmus ohba* because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting luciferase activity and independence thereof to pH and temperature changes; (B) the general tolerance of luciferase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any luciferase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the

scope of the claims broadly including vectors and host cells comprising any gene encoding luciferase which emit light having a λ_{max} of 536-635 nm which does not substantially depend on either pH or temperature or any red-emitting luciferase from rail road worm, green-emitting luciferase from rail road worm, green-emitting luciferase from *Rhagophthalmus ohba* or any orange-emitting luciferase from *Rhagophthalmus ohba*. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of vectors and host cells having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 13-18 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated mammalian cells transformed with the one or more luciferase genes (see rejection above), does not reasonably provide enablement for mammalian cells within a mammal that have been transformed with the one or more luciferase genes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

make and use the invention commensurate in scope with these claims.

Claims 13-18 and 22 are so broad as to encompass mammalian cells transformed with specific nucleic acids, including cells in *in vitro* culture as well as cells within a mammal. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of host cells broadly encompassed by the claims. While methods for transforming cells *in vitro* are well known in the art, methods for successfully transforming cells within complex multicellular organisms such as mammals are not routine and are highly unpredictable. Furthermore, methods for producing a successfully transformed cell within one multicellular organism are unlikely to be applicable to transformation of other types of multicellular organisms as multicellular organisms vary widely. However, in this case the disclosure is limited to only host cells *in vitro*. Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including the use of host cells within a multicellular organism for the production of polypeptide. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ

19 24 (CCPA 1970)). Without sufficient guidance, expression of genes in a particular host cell and having the desired biological characteristics is unpredictable the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is suggested that applicants limit the claims to "An isolated mammalian cell …".

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 7, 10-15 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Wood et al. (2008/0090291) as evidenced by Viviani et al. (US Patent 7,276,363).

Wood et al. teach gene constructs for expression in mammalian cells of several synthetic click beetle luciferase genes including a green-emitting gene and a red-emitting gene (see paragraph [0238] and Table 8). Viviani et al. evidence that the wavelength of the light produced by click beetle luciferase genes does not substantially depend on pH (see column

3, lines 22-28). Wood et al. teach that suitable mammalian expression vectors include Kozak sequences and introns (paragraphs [0014] and [0079]. Wood et al. further teach the use of at least two such luciferase genes together within a mammalian cell (see for example paragraphs [0020], [0114], [0117], [0118], and [0296]) and teach that in such assays the multiple reporter genes each include separate promoters including a constitutive promoter and a promoter to be assessed (see paragraph [0296]).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wood et al. (2008/0090291) in view of Viviani

et al. (US Patent 7,276,363) or Viviani et al (Reference 13 of applicant's IDS of 2/06).

Wood et al. is discussed above. Wood et al. does not teach constructs for mammalian expression of a luciferase gene encoding a red-emitting luciferase from rail road worm, a green-emitting luciferase from rail road worm, a green-emitting luciferase from *Rhagophthalmus ohba* or an orange-emitting luciferase from *Rhagophthalmus ohba*.

Viviani et al. (US Patent 7,276,363) teach genes encoding a red-emitting luciferase from rail road worm and a green-emitting luciferase from rail road worm and that that the wavelength of the light produced by these luciferases does not substantially depend on pH.

Viviani et al (Reference 13 of applicant's IDS) teach genes encoding a red-emitting luciferase from rail road worm, a green-emitting luciferase from rail road worm, a green-emitting luciferase from *Rhagophthalmus ohba* and an orange-emitting luciferase from *Rhagophthalmus ohba* and that that the wavelength of the light produced by these luciferases does not substantially depend on pH.

Wood et al. clearly teach that any luciferase gene can be used as a reporter and suggest the expression of such genes Therefore, it would have been obvious to one of ordinary skill

in the art to substitute the luciferase genes of the constructs of Wood et al. with the luciferase genes of Viviani et al. (US Patent 7,276,363) or Viviani et al (Reference 13 of applicant's IDS). Furthermore, if these genes did not express well it would have been obvious to one of ordinary skill in the art to modify them using the methods taught by Wood et al. to increase the expression of luciferase genes in mammalian cells.

Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wood et al. (2008/0090291) as applied to claims 7, 10-15 and 22 above or Wood et al. (2008/0090291) in view of Viviani et al. (US Patent 7,276,363) or Viviani et al (Reference 13 of applicant's IDS of 2/06) as applied to claim 9 above, and further in view of Zock et al. (US PG-PUB 2006/0265137).

Wood et al. (2008/0090291), Viviani et al. (US Patent 7,276,363) and Viviani et al (Reference 13 of applicant's IDS) are discussed above and teach or make obvious mammalian cells including expression vectors for one or two luciferase reporter genes fused to a heterologous promoter. They do not explicitly teach cells including at least three luciferase reporter genes.

Zock et al. teach mammalian cells which comprise a reporter set comprising at least three fluorescent reporter molecules

(see paragraphs [0012] and [0022]) and that such cells have use for assaying many complex biological systems.

Therefore, it would have been obvious to one of ordinary skill in the art to select three different luciferase genes as taught by Wood et al. (2008/0090291), Viviani et al. (US Patent 7,276,363) or Viviani et al (Reference 13 of applicant's IDS) which encode luciferases having different λ_{max} values, such that the light emitted is distinguishable as the three reporter of the assays disclosed by Zock et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed, can be reached at (571) 272-0934. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Rebecca Prouty/
Primary Examiner
Art Unit 1652